

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 05 DEC 2005

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Applicant's or agent's file reference PAM-017-PCT		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/EP2004/009351		International filing date (day/month/year) 20.08.2004		Priority date (day/month/year) 21.08.2003
International Patent Classification (IPC) or national classification and IPC B01J19/00				
Applicant PAMGENE B.V. et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 4 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input checked="" type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 13.06.2005		Date of completion of this report 01.12.2005		
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Nazario, L Telephone No. +49 89 2399-8137		



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/009351

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-15 as originally filed

Claims, Numbers

1-24 filed with telefax on 13.06.2005

Drawings, Sheets

1/2, 2/2 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/009351

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
- ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☐ not complied with for the following reasons:
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-24
Inventive step (IS)	Yes: Claims	
	No: Claims	1-24
Industrial applicability (IA)	Yes: Claims	1-24
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/009351

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the report

The present written opinion has been established as if the priority has been validly claimed and therefore, WO-A-04 089532 has not been considered as part of the state of the art.

Re Item IV

Lack of unity of invention

1. The following groups of inventions have been found:

1. Claims: 1, 2, 5-10 (all in part), 11-13, 14-17 (all in part), 18, 19-24 (all in part)

Independent claim 1 (and dependent claims 4-9 and 10) relates to systems comprising a porous reaction substrate having a flat top and bottom surface in which the diameter of the pores is comprised between 10 micron and 10 nm and further comprising a first rigid support member bonded to the porous layer. This latter component comprises holes extending through the whole layer.

2. Claims: 3, 4, 5-10 (all in part), 11-13, 14-17 (all in part), 18, 19-24 (all in part)

Independent claims 3 and 4 (and dependent claims 4-9) relate to systems comprising a porous reaction substrate having a flat top and bottom surface in which the diameter of the pores is comprised between 10 μ m and 10 nm. Some of the pores of the substrate are masked by filling them with a polymer, so as to form borders of the reactor zones.

2. The only common/corresponding technical feature between the independent claims of the two groups is the provision of a porous reaction substrate having a flat top and bottom surface and in which the diameter of the pores is comprised between 10 μ m and 10 nm. Such a concept is not novel and is well known in the art and in particular it is disclosed in the documents cited in the search report. For example, WO 95 1175 (figure 1, page 14, line 6 to page 15, line 19) and US-B1-6 225 131 (col. 5, line 21 to col. 7, line

30) disclose such substrate materials.

Furthermore, the two groups solve different technical problems that are not linked by an inventive concept. Group 1 attempts to solve the problem of how to provide mechanical stability; and group 2 addresses the problem of how to define independent reaction areas within the substrate.

3. Therefore, the requirements of Rule 13 (1) and (2) PCT are not fulfilled.

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. The following document (D) is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 95 11755 A
D2: WO 01 87484 A
D3: WO 03 034026 A
D4: WO 03/052420 A
D5: WO 01/19502 A
D6: US-A-5 980 709

2. The independent claims state that the expression "essentially parallel pores" also includes any through-going channel and branched interconnecting pores. Such an amendment does not restrict the scope of the claims and introduces a contradiction in the claim, i.e. essentially parallel pores cannot be branched and interconnecting.

3. D1-D4 disclose porous substrates which are used in systems for conducting chemical and/or biochemical reactions. The substrates therein disclosed comprise flat top and bottom surfaces. The pores may be parallel or have a tortuous path and their diameters of the pores fall within the range disclosed in independent claim 1. Furthermore, the substrates are bonded (e.g. thermal bonding) to a rigid support that comprises a plurality of holes which also define reactor zones. Part of holes (or the whole area) may be

covered. The support are may be inorganic (e.g. nanoporous glass) or organic (e.g. polymer gels) and may be transparent so that the system may be used in combination with a detector (e.g. fluorescence detector). The devices may be used in the synthesis or in assay polynucleotides or other biological reactions. (see passages cited in the International Search Report.)

Therefore, the subject-matter of claims 1, 2, 5 -24 is not novel and does not fulfill the requirements of Article 33(2) PCT.

4. D5 and D6 disclose devices comprising a porous membrane which has been treated in order to provide non-porous areas which define reaction zones. The membrane may be treated by filling the pores of the perimeter areas with a polymer. D5 clearly discloses that the membrane may be placed between two supporting structures each comprising through going holes aligned with each other. The use in biotechnology, and in particular in high-throughput screening, is also disclosed. (See passages cited in the International Search Report.)

Therefore, the subject-matter of claims 3-24 is not novel and does not fulfill the requirements of Article 33(2) PCT.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D6 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

1. The following claims do not fulfill the requirements of Article 6 PCT:
 - 1.3. For the reasons stated in point V - 2, the claims do not fulfill the requirements of clarity.

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/EP2004/009351

- 1.2. Claim 7 appears to be redundant (see present claim 10).
- 1.3. Claims 13 and 14 do not further characterise the system to which they refer back to.
These claims only include process features.

Claims (retyped)

1. System for conducting chemical and/or biochemical reactions, comprising a reaction substrate with a multiplicity of reactor zones, said reaction substrate having a substantially flat top surface and a substantially flat bottom surface, the reaction substrate being porous with a multiplicity of essentially parallel pores enabling liquid flow through, wherein said essentially parallel pores include through-going oriented channels including discrete and branched pores which are connected to adjacent pores in the substrate, said pores having a diameter of 10 μm to 10 nm, characterised in that said flat top surface is bonded to the bottom of a first rigid support, said rigid support comprising a multiplicity of through going holes extending from the top of said rigid support to the bottom of said rigid support, and said through going holes defining the reactor zones.
2. System according to the previous claim, wherein a subset of said holes are, possibly reversibly, masked.
3. System for conducting chemical and/or biochemical reactions, comprising a reaction substrate with a multiplicity of reactor zones, said reaction substrate having a substantially flat top surface and a substantially flat bottom surface, the reaction substrate being porous with a multiplicity of essentially parallel pores enabling liquid flow through, wherein said essentially parallel pores include through-going oriented channels including discrete and branched pores which are connected to adjacent pores in the substrate, said pores having a diameter of 10 μm to 10 nm, characterised in that part of said pores are masked by filling said pores with a masking polymer, the masked pores defining the outer borders of the reactor zones.
4. System for conducting chemical and/or biochemical reactions, comprising a reaction substrate with a multiplicity of reactor zones, said reaction substrate having a substantially flat top surface and a substantially flat bottom surface, the reaction substrate being porous with a multiplicity of essentially parallel pores enabling liquid flow through, wherein said essentially parallel pores include through-going oriented channels including discrete and branched pores which are

connected to adjacent pores in the substrate, said pores having a diameter of 10 μm to 10 nm, characterised in that

- (i) part of said pores are masked, by filling said pores with a masking polymer the masked pores defining the outer borders of the reactor zones; and
 - (ii) said flat top surface is bonded to the bottom of a first rigid support comprising a multiplicity of through going holes extending from the top of said rigid support to the bottom of said rigid support, and said through going holes defining the reactor zones.
5. System according to any of the previous claims, wherein chemical moieties, chemical building groups, chemical monomers, molecules or polymers are anchored to the walls of said pores.
 6. System according to any of claims 2 to 5, wherein said masking is carried out by a masking polymer, including polyacrylamide, photocrosslinkable masking polymers and photoreactive glues.
 7. System for conducting chemical and/or biochemical reactions according to any of the previous claims, wherein said reaction substrate is optically transparent allowing said chemical and/or biochemical reactions to be monitored optically.
 8. System according to any of the previous claims, wherein said chemical and/or biochemical reactions are polymer synthesis reactions, including nucleotide synthesis reactions, peptide synthesis reactions, and sugar polymer synthesis reactions.
 9. System according to any of the previous claims, wherein said reaction substrate is made of an organic or inorganic material, such as aluminium oxide.
 10. System according to any of the previous claims, wherein said reaction substrate is optically transparent or translucent.
 11. System according to claims 1, 2, or 4 wherein said rigid support is bonded to the

reaction substrate by moulding, glueing, thermal bonding, laser welding, chemical bonding and the like.

12. System according to the claims 1, 2 or 4 wherein, said rigid support is a chemical and/or temperature resistant material, such as Topas ®.
13. System according to the claims 1, 2, or 4, wherein said holes of said rigid support defining the reactor zones contain reaction components.
14. System according to claim 13, wherein said reaction components are chosen from the group comprising a solvent, reagent, wash solution, enzymes or monomer used for the polymer synthesis reaction.
15. System according to any of the previous claims comprising a means for applying a pressure.
16. System according to any of the previous claims comprising a means for inducing a reversible flow through said reaction substrate.
17. System according to any of the previous claims, comprising a reaction manifold for selectively delivering particular solvents, reagents, wash solutions, enzymes and/or monomers to said reaction zones.
18. System according to the claims 1, 2 or 4, wherein said rigid support has at least 96, 384 or 1536 holes or reactor zones.
19. System according to any of the previous claims wherein the bottom surface of said reaction substrate is bonded to the top of a second rigid support, said second rigid support having through going holes extending from the top of the second rigid support to the bottom of the second rigid support, and said holes of the second rigid support are aligned with the holes of the first rigid support.
20. Use of the system according to any of the previous claims for conducting chemical and biochemical reactions, including the synthesis of polymers.

21. Use of the system according to any of the previous claims, wherein said polymers are oligonucleotides, peptides or sugar chains.
22. Use of the system according to any of the previous claims for synthesising in parallel different polymers.
23. Process to synthesise polymers, characterised in that said polymers are attached to the pores of a system according to any of the previous claims.
24. Apparatus for conducting chemical and/or biochemical reactions comprising a system according to any of the previous claims, an incubation device for holding said system, a loading station, possibly a dispensing and aspiration station, possibly a pressure or vacuum application station, and possibly a reading station.